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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

18M1/0606

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ART UNIT	PAPER NUMBER
RABIN, E	
1816	7

DATE MAILED: 06/06/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire — 3 — month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-45 is/are pending in the application.
Of the above, claim(s) 16, 17, 21, 22, 25, 26, and 29-45 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) ~~1-15~~, 18-20, 23, 24, 27, and 28 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5 & 6
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1996-404-498/40517

DETAILED ACTION

Response to Amendment

1. Effective February 7, 1998, the location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1644, Technology Center 1600.

2. Applicant's amendment was received December 12, 1997 as Paper No. 9. Claim 10 has been canceled. Claims 1- 9 and 11-45 are pending. Claims 16, 17, 21, 22, 25, 26, and 29-45 are held to be withdrawn from further consideration, as being drawn to a non-elected invention. Claims 1-9, 11-15, 18-20, 23, 24, 27, and 28 are currently under examination.

3. The text of those sections of title 35 USC not included in this Action can be found in the prior office action (Paper No. 7).

4. Any rejection not present in this office action is considered withdrawn.

5. Claims 1, 8, 13, and 18 are objected to under 37 C.F.R. § 1.821(d) for failing to recite the SEQ ID NOS. Claims 1, 8, 13, and 18 have been amended to recite particular sequences (CDRs) and thus recite *parts* of longer amino acid sequences which describe the light and heavy chain variable regions and which are identified by SEQ ID NOS: 12 and 15, respectively. The sequences recited in the claims have been referred to specifically as defined sequences in Figures 7 and 9 and thus do not represent new matter. However, the sequences recited in the claims must be identified. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in

the "Sequence Listing," see MPEP 2422.03. Alternatively, Applicant can assign new SEQ ID numbers to the six sequences recited for CDRs 1, 2, and 3 of the light and heavy chains and submit the sequences in a manner that complies with the requirements of the sequence rules.

In addition, the specification is objected to under 37 C.F.R. 1.821 (d) for failing to disclose SEQ ID Nos. for the CDRs in the brief descriptions for Figures 7 and 9, *e.g.*, "for the light chain: CDR 1, residues 44-59 of SEQ ID NO: 12."

11. Claims 1-9, 11-15, 18-20, 23, 24, 27, and 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Queen *et al.* [U. S. Patent 5,530,101 (102(e) Date: Dec 28 1988)] in view of Lazarovits *et al.* [J. Immunol. 151 (11): 6482-6489 (Dec 1993)], for the same reasons as set forth in Paper No. 7.

6. Applicant's arguments filed December 12, 1997 as Paper No. 9 have been fully considered, but they are not persuasive.

Applicant argues that Queen *et al.* do not teach humanized immunoglobulins having binding specificity for $\alpha 4\beta 7$ integrin. Applicant argues that Lazarovits *et al.* provide no means for carrying out immunotherapy. Applicant argues that thus there is no motivation for combining the references and no teaching of expectation of success. Applicants further argue that in any case, there is no teaching of the CDR sequences of the Act-1 antibody.

7. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or *in the knowledge generally available to one of ordinary skill in the art.* See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it was well known in the art to use antibodies directed to adhesion molecules or their respective ligands to treat inflammation by preventing the adhesion molecule - ligand interaction. The causative mechanisms by which inflammation occurs be it trauma, graft rejection, autoimmune disease such as rheumatoid arthritis, etc., all result in the same effect, that is, inflammation, which one of ordinary skill in the art would have recognized as being treatable by antibody therapy. Thus, it would have been obvious at the time of the invention to make a therapeutic reagent comprising an antibody capable of acting as an antagonist, *i.e.*, capable of inhibiting an interaction between an adhesion molecule and its ligand. Because a goal of clinical medicine is to treat human patients, it would have been obvious to make a therapeutic reagent that would have a reasonable expectation of success in human patients. Queen *et al.* teach that humanized antibodies have at least three potential advantages over mouse or in some cases chimeric antibodies for use in human therapy: (1) because the effector portion is human, they interact better with other parts of the human immune system, (2) they are less immunogenic, (3) they have a half-life more similar to naturally occurring human antibodies allowing smaller and less frequent doses to be given (Column 16, Lines 6-26, in particular). In addition, Queen *et al.* teach that humanized Igs can be more economically produced (Column 68, Lines 12-14, in particular).

Lazarovits *et al.* teach Act-1 mAb and that the antigen recognized by Act-1 is $\alpha 4\beta 7$, the receptor for fibronectin and vascular cell adhesion molecule-1. On Page 6487, Last

paragraph, cited in Paper No. 7, Lazarovits *et al.* teach that "since integrins such as α4β7 deliver transmembrane signals to the T cells via tyrosine phosphorylation, and since these signals are mitogenic, it is reasonable to suggest that α4β7 expression may also lead to signals that perpetuate and augment the rheumatoid disease process. It is possible that interference with α4β7 may be beneficial in the immunotherapy of rheumatoid arthritis." Lazarovits *et al.* offers that it is reasonable to assume that the expression of the adhesion molecule, α4β7, is important, for example, in rheumatoid arthritis. Given the knowledge in the art of the success of antibodies specific for adhesion molecules acting as antagonists and inhibiting inflammation *in vivo*, one of ordinary skill in the art would have been motivated to generate a humanized anti-α4β7 antibody. A 103 rejection does not require that the reference show that an anti-α4β7 antibody would be successful in therapy, only that there is a reasonable expectation that there would be success. Knowledge in the art and Lazarovits *et al.* teach that there would be.

In response to the argument that there is no teaching of the CDR sequences of the Act-1 antibody. Whether or not Queen *et al.* teach the sequence and humanizing of Act-1 in particular is irrelevant to their having anticipated the CDR-grafted Act-1 of the instant application. Queen *et al.* teach humanized immunoglobulin (Ig) chains having one or more complementarity determining regions (CDRs) from a donor Ig and a framework region from a human Ig. Queen *et al.* teach that a humanized light and heavy chain can be used to form a complete humanized Ig or antibody, having two light/heavy chain pairs, with or without partial or full-length human constant regions. Queen *et al.* teach that to form the humanized variable region, amino acids in the human acceptor sequence will be replaced by the corresponding amino acids from the donor sequence if they are in a CDR (Column 2, Lines 35-67, in particular). Queen *et al.* teach that the extent of the framework region and CDR's have been precisely defined by Kabat *et al.* (Column 11, Lines 38-42, in particular). Queen *et al.* further teach that other

substitutions are required in the human framework in order for the antibody to "be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen" (Column 3, Lines 33-36, in particular). Queen further outlines other categories wherein amino acids in the human acceptor sequence are replaced by the corresponding amino acids from the donor sequence (Column 3, Lines 1-31, in particular). Queen *et al.* teach that in some cases, it may be considered preferable to use light and heavy chains from the same human antibody as acceptor sequences to be sure the humanized light and heavy chains will make favorable contacts with each other, *e.g.,*Eu, Lay, Pom (Column 13, Lines 39-56, in particular). Queen *et al.* teach that typically one of the 3-5 most homologous heavy chain variable region sequences in a representative collection of at least about 10 to 20 distinct heavy chains will be chosen as acceptor to provide the heavy chain framework, and similarly for the light chain and that the selected acceptor immunoglobulin chain will most preferably have at least about 65% homology in the framework region to the donor immunoglobulin (Column 13, Lines 32-40, in particular).

It would have been obvious to one of ordinary skill in the art to use Queen's method of producing humanized antibody and art-known techniques of molecular cloning to make humanized antibodies specific for $\alpha 4\beta 7$. Queen *et al.* teach that once an antibody (nonhuman) is chosen, following their criteria, *i.e.*, choosing the human framework, choosing which particular amino acids should be donor or acceptor, and following their reasoning for making changes, any antibody can be humanized. Queen *et al.* teach expression vectors, a recombinant expression system capable of encoding said variable region which comprises said encoding nucleotide sequence in operable linkage with control nucleotide sequences compatible with a recombinant host cell, and recombinant host cells. Queen *et al.* teach a method to produce a protein which comprises the variable region of a light chain and/or heavy chain of an immunoglobulin wherein the method comprises culturing said host cells wherein expression is effected

to produce said protein and recovering said protein from the culture. Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to be motivated to use the methods of Queen and the mAb taught by Lazarovits *et al.* to make humanized Act-1 antibody including fragments, multimers, fusion proteins and conjugates, with the expectation that an antibody would be successfully obtained and useful for therapeutic treatments, for diagnostic assays, and for purifying ligand.

8. No claims are allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Rabin, Ph.D. whose telephone number is (703) 305-6811. The examiner can normally be reached on Monday through Thursday from 7:30 AM to 6:00 PM.

11. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The FAX number for this Technology Center is (703) 305-3014 or (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center receptionist whose telephone number is (703) 308-0196.

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March 4, 1998

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